REMARKS

Applicants appreciate the examination of the present application as evidenced by the Office Action dated June 10, 2009 (hereinafter, the "Office Action"). Claims 1-27 and 31-40 are pending in the application. Claims 9, 10, 16-18, and 40 have been withdrawn from consideration. Claims 1-8, 11-15, 19-27, and 31-39 stand rejected.

The Examiner asserts that a certified copy of the foreign priority application must be separately filed before Applicants can claim priority as of that application's September 23, 2003 filing date. Applicants note, however, that the present application is a national stage application filed under 35 U.S.C. § 371. As such, the priority document should have been requested from the International Bureau and placed into the national stage file (per M.P.E.P. § 1893.03(c)). Indeed, a certified copy of the priority application was added to the file wrapper on March 22, 2006 and is presently accessible through the USPTO's website.

Applicants have amended pending Claims 1-3 and 5 herein to further clarify the patentable distinctions of the present invention. Likewise, Claims 31-33 have been amended to correct minor typographical errors and to further clarify the recited methods. Finally, new Claims 41 and 42 have been added to further clarify certain embodiments of the claimed invention. Support for these amendments can be found throughout the specification.

Applicants respectfully traverse the aforementioned rejections for at least the following reasons. For the convenience of the Examiner, the issues are addressed in the order in which they were presented in the Office Action.

NOVELTY

Claims 1-6, 11, 15, 19-27 and 31-36 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 6,419,896 to Vogelstein et al. (hereinafter "Vogelstein").

Claims 1-6, 11, 15 and 19-27 stand rejected under 35 U.S.C § 102(a) as allegedly being anticipated by Matzuk et al. (BIOL. REPRO. 69:338-346 (July 2003) (available online April 2, 2003)) (hereinafter "Matzuk").

Anticipation under 35 U.S.C. § 102 requires that each and every element of the claim be found in a single prior art reference. *W. L. Gore & Associates Inc. v. Garlock, Inc.*, 721

F.2d 1540, 1554, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983). A finding of anticipation further requires that there must be no difference between the claimed invention and the disclosure of the cited reference as viewed by one of ordinary skill in the art. *See Scripps Clinic & Research Foundation v. Genentech Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991). Additionally, the cited prior art reference must be enabling, thereby placing the allegedly disclosed matter in the possession of the public. *In re Brown*, 329 F.2d 1006, 1011, 141 U.S.P.Q. 245, 249 (C.C.P.A. 1964). Thus, the prior art reference must adequately describe each and every element of the claimed invention such that a person of ordinary skill in the art could make and use the invention.

Applicants respectfully submit that neither Vogelstein nor Matzuk anticipates the claimed invention.

A. Vogelstein

Vogelstein discloses the use of recombinant tumor cells expressing an exogenous marker protein (namely β-hCG) as a means for "quantifying experimental tumor growth" (Column 3, lines 56-59)—by monitoring the level of marker protein found in the affected animal's urine, Vogelstein and his colleagues are able to extrapolate how many tumor cells are present (and thus how much the tumor has grown since the initial injection of tumor cells). In order to obtain an accurate measure of tumor cell proliferation, Vogelstein relies on the constitutive expression of the exogenous marker protein. Such reliance is highlighted by Vogelstein's list of preferred promoters, which contains a litany of high-level, constitutive expressers: CMV, SV40, RSV, β-actin promoter and GADPH (Column 4, lines 47-52).

Vogelstein's focus on the use of promoters that cause high-level, constitutive expression is understandable. If the level of marker protein is allowed to fluctuate to any significant degree, it becomes impossible to claim that increases/decreases in the amount of marker protein are directly correlated to changes in the number of tumor cells present. Thus, constitutive expression is vital to Vogelstein's invention.

Accordingly, Vogelstein's teachings do not provide an enabling disclosure for nucleic acid constructs wherein a reporter protein is inducibly expressed.

Nucleic Acid Constructs

A nucleic acid construct of Claim 1, which recites a nucleic acid construct encoding both a "secretable or excretable reporter protein" and "an inducible promoter that drives the production or expression of said reporter protein," is clearly not anticipated by Vogelstein's constitutively-expressed β-hCG constructs.

Nor are Claims 2-6, 11, 15 or 34-36. Each of the aforementioned dependent claims is patentable over Vogelstein at least by virtue of their depending from an allowable claim. Moreover, many of these claims are separately patentable over Vogelstein. For example, Claim 11 recites a nucleic acid construct that encodes a modified β-hCG. And, contrary to the Examiner's assertion at page 4 of the Office Action, merely using a construct that contains a promoter element upstream of β-hCG does not result in the secretion/excretion of a modified β-hCG. Similarly, Vogelstein fails to anticipate Claim 36 because it fails to disclose the use of transgenic animals.

Newly-added Claims 41 and 42 clearly fall outside the scope of Vogelstein's teaching. Unlike Vogelstein's constructs, which are constitutively-expressed in recombinant tumor cells, the constructs recited in Claims 41 and 42 only produce or express reporter protein in response to disturbances in the homeostatic state of DNA, pro-apoptotic stimuli, disease onset, etc, as recited therein. Moreover, Claim 42 recites a construct comprising a peptide tag, something which does not exist in Vogelstein's constitutively-expressed constructs.

Cell Lines / Host Cells

Because Vogelstein fails to anticipate a nucleic acid construct of Claim 1, it can anticipate neither a cell line of Claim 20, nor the host cells of Claims 19, 26 and 27.

Transgenic Non-Human Animals

Vogelstein fails to anticipate Claims 21-25 and 36 for at least two reasons: 1) because it fails to disclose a nucleic acid construct according to Claim 1, and 2) because it fails to disclose the expression of such a construct in transgenic non-human animals. Vogelstein merely teaches the injection of animals with recombinant tumor cells, not the creation of a transgenic animal expressing a nucleic acid construct of Claim 1.

Gene Activation Assays

Vogelstein fails to anticipate Claims 31-33 for at least two reasons: 1) because it fails to disclose a nucleic acid construct according to Claim 1, and 2) because it's only teaching regarding the use of its nucleic acid construct is as a way of quantifying tumor cell growth.

B. Matzuk

Like Vogelstein, Matzuk relies on the constitutive expression of β-hCG. Matzuk discloses the use of the mouse metallothionein 1 promoter (mMT-1) to "generate multiple lines of transgenic mice that overexpress[] either one or both subunits of hCG" (Abstract, emphasis added). Although Matzuk describes two distinct populations of mice—low-level overexpressers and high-level overexpressers—that distinction is related to the number of copies of the transgene that each mouse carries (*See, e.g.*, page 339). Matzuk is very clear that even the low-level overexpressers produce hCG constitutively: "Thus, constitutive low-level expression of hCG causes progressive infertility of unknown etiology in both male and female transgenic mice." (page 340)

Accordingly, Matzuk's teachings do not provide an enabling disclosure for nucleic acid constructs wherein a reporter protein is inducibly expressed.

Nucleic Acid Constructs

The nucleic acid constructs of Claims 1-6, 11, 15, 41 and 42 are patentable over Matzuk because each construct encodes "an inducible promoter that drives the production or expression of [the] reporter protein" (Emphasis added). Furthermore, many of these claims recite additional elements that are not found in Matzuk (e.g., a modified β-hCG or a peptide tag).

Cell Lines / Host Cells

Because it does not disclose a nucleic acid construct of Claim 1, Matzuk fails to anticipate the host cells of Claims 19, 26 and 27. Likewise, Matzuk fails to disclose a cell line according to Claim 20. Indeed, Matzuk fails to disclose any cell line at all.

Transgenic Non-Human Animals

Matzuk fails to anticipate Claims 21-25 because it does not disclose a nucleic acid construct according to Claim 1.

NON-OBVIOUSNESS

Claims 1-8, 11, 13-15, 19-27 and 31-39 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Vogelstein in view of WIPO Patent Publication No. 2000/079264 to Beaudet et al. (hereinafter "Beaudet").

Claim 12 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Vogelstein in view of Beaudet, and further in view of Aprelikova et al. (JBC 276:25,647-25,650 (2001)) and Hermeking et al. (MOL. CELL. 1:3-11 (1997)).

As stated in the recently published Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex, Inc.* (Federal Register Vol. 72, No. 195, 57526-57535, 57526), "the Supreme Court reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co*...." Hence, and as long established under that framework, to establish a *prima facie* case of obviousness, three requirements must be satisfied (M.P.E.P. § 2143). First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated one of ordinary skill in the art to modify a reference or to combine references. *In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the proposed modification or combination of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Third, the prior art reference or combination of references must teach or suggest all of the limitations of the claims. *See In re Wilson* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art").

Applicants respectfully submit that, not only would one of ordinary skill in the art

have lacked motivation to combine the cited references, Vogelstein itself actually dissuades such a combination. Moreover, even if the cited references were combined, the resulting hypothetical construct would *not* be that of the claimed invention.

A. Vogelstein and Beaudet

As was previously discussed, Vogelstein teaches the use of recombinant tumor cells that constitutively overexpress an exogenous marker protein. Indeed, the entire premise of Vogelstein's invention is that the recombinant tumor cells constitutively express the marker protein at a stable level—if Vogelstein's constructs allowed for the differential expression of marker protein, fluctuations in the amount of marker protein could not be directly attributed to an increase/decrease in the number of tumor cells.

In sharp contrast, Claim 1 recites a nucleic acid construct that encodes both "a secretable or excretable reporter protein" and "an inducible promoter that drives the production or expression of said reporter protein." Likewise, Claim 41 recites a construct wherein the reported protein is only produced or expressed in response to disturbances in the homeostatic state of DNA, pro-apoptotic stimuli, disease onset, etc.

Thus, even if one of ordinary skill in the art were somehow motivated to combine the teachings of Beaudet and Vogelstein, he/she could not create a construct of the claimed invention. Adding a peptide tag (myc, or otherwise) to Vogelstein's construct merely yields a constitutively-expressed marker protein with a tag. That is clearly not the claimed invention.

Accordingly, Applicants respectfully submit that Claims 1-8, 11, 13-15, 19-27, 31-39 and 41-42 are patentable over Vogelstein and Beaudet.

B. Aprelikova and Hermeking

Claim 12 is patentable over Vogelstein, Beaudet, Aprelikova and Hermeking because, among other things, one having ordinary skill in the art would have no motivation to combine them. On the off chance that one skilled in the art did happen to read Vogelstein along with Aprelikova and Hermeking, he/she would likely be left perplexed—none of the cited secondary references have anything to do with Vogelstein. Nothing in any of the cited references provides even a hint that they might be beneficially combined.

If anything, Vogelstein teaches that the 14-3-3σ promoter is a poor choice for use in

its construct. The epigenetic silencing of 14-3-3σ by CpG methylation has been shown in a wide variety of carcinomas (for a good review, see Lodygin and Hermeking, CELL RESEARCH 15:237-246 (2005)), meaning that any marker protein placed downstream of a 14-3-3σ promoter is unlikely to be produced in the recombinant tumor cells of Vogelstein's invention. As such, one skilled in the art would have no motivation to combine Vogelstein with either Aprelikova or Hermeking.

Accordingly, Applicants respectfully submit that Claim 12 is patentable over the cited references.

PARTICULARITY

Claims 31-33 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Applicants have amended each of the aforementioned claims to more particularly claim the recited methods and respectfully submit that each claim is now in condition for allowance.

CONCLUSION

Having addressed the Examiner's concerns in full, Applicants respectfully submit that the present application is in condition for allowance and the same is earnestly solicited. The Examiner is encouraged to telephone the undersigned at 919-854-1400 for resolution of any outstanding issues.

Respectfully submitted,

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I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on September 10, 2009.

Betty-Lou Rosser